

STATE-OF-THE-ART PAPER

Iron Overload Cardiomyopathy

Better Understanding of an Increasing Disorder

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The prevalence of iron overload cardiomyopathy (IOC) is increasing. The spectrum of symptoms of IOC is varied. Early in the disease process, patients may be asymptomatic, whereas severely overloaded patients can have terminal heart failure complaints that are refractory to treatment. It has been shown that early recognition and intervention may alter outcomes. Biochemical markers and tissue biopsy, which have traditionally been used to diagnose and guide therapy, are not sensitive enough to detect early cardiac iron deposition. Newer diagnostic modalities such as magnetic resonance imaging are noninvasive and can assess quantitative cardiac iron load. Phlebotomy and chelating drugs are suboptimal means of treating IOC; hence, the roles of gene therapy, hepcidin, and calcium channel blockers are being actively investigated. There is a need for the development of clinical guidelines in order to improve the management of this emerging complex disease. (J Am Coll Cardiol 2010; 56:1001–12) © 2010 by the American College of Cardiology Foundation

Iron is an essential element that forms an important component of metabolic and biological processes, but when present in excess, it can produce tissue damage due to oxidative stress (1). Excess body iron may accumulate in liver, spleen, heart, bone marrow, pituitary, pancreas, and the central nervous system, causing damage to these organs. Iron overload cardiomyopathy (IOC) results from the accumulation of iron in the myocardium, and it is the leading cause of death in patients receiving chronic blood transfusion therapy (2). The incidence of IOC is increasing worldwide, and it is usually managed by cardiologists. Noteworthy has been its increase in individuals with hematologic malignancies, especially with the increased use of treatments such as bone marrow transplant and stem cell therapy (3). Furthermore, as patients with sickle cell disease and thalassemia live longer, IOC incidence rises. It has been documented that adequate medical therapy can reverse IOC when it is diagnosed before end-stage heart failure occurs (4), thus underscoring the importance of early detection of IOC. Thus, it is critical for cardiology care providers to keep their knowledge updated on managing IOC to take advan-

tage of recent progress in this area. In this paper, the current status of diagnosis of IOC, particularly using imaging modalities and updated therapeutic approach for IOC, is reviewed.

Etiology

IOC has been defined as the presence of systolic or diastolic cardiac dysfunction secondary to increased deposition of iron in the heart independent of other concomitant processes (1). Excess iron accumulation in the body usually takes place either by increased gastrointestinal (GI) iron absorption (hemochromatosis) or excess administration of exogenous iron by dietary sources or red blood cell (RBC) transfusions (hemosiderosis). These conditions are described in Table 1.

Increased iron absorption. Hereditary hemochromatosis (HH) is an autosomal disorder in which mutations of specific genes involved in iron metabolism cause iron overload in the body, with increased GI absorption (5,6). It has been divided into 4 subtypes as described in Table 1. The association of IOC with HH has been well characterized (7,8). Increased GI absorption with a normal diet is also observed in porphyria cutanea tarda (9); chronic liver disease, including nonalcoholic fatty liver disease (10); hepatitis B (11) or C (12); and in ineffective erythropoiesis, as seen in sideroblastic anemia (13) and severe thalassemia (14).

Excess administration of exogenous iron. Sub-Saharan Africans have a high dietary iron intake as a result of drinking traditional beers fermented in steel drums (African iron overload) (15). This mechanism of iron overload was

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Abbreviations and Acronyms

CC	= calcium channel blocker
CT	= computed tomography
GE	= gradient echo
GI	= gastrointestinal
HH	= hemochromatosis
IOC	= iron overload cardiomyopathy
LTCC	= L-type calcium channel
LV	= left ventricular
MRI	= magnetic resonance imaging
RBC	= red blood cell
SE	= spin echo
TE	= echo time

initially thought to be the etiology of hepatic carcinoma and cardiomyopathy in these patients, but other reports suggest that environmental factors superimposed on genetic predisposition may be a better explanation for the development of these conditions (16,17).

Parenteral iron administration.

Chronic blood transfusion is the cornerstone of treatment for hereditary anemias such as thalassemia and sickle cell disease. A unit of packed RBCs consists of 200 to 250 mg of elemental iron that accumulates in the body because there is no active excretion of iron. Over long periods of repeated transfusions, iron overload occurs with deposition of

iron in multiple organs. Earlier detection of these hereditary anemias is associated with a decreased mortality due to improved treatment, but treatment often requires persistent chronic transfusion, one of the reasons for an increasing incidence of iron overload (18–20).

Pathogenesis

Iron kinetics is illustrated in Figure 1 (21–23). Deposition of iron in the heart is a gradual process and depends on the increasing levels of serum iron. Under normal iron homeostasis, cardiac iron is regulated through transferrin-mediated uptake mechanisms. During iron overload, transferrin is saturated, and nontransferrin-bound iron is released into the circulation and enters cardiac myocytes in the ferrous form through L-type calcium channels (LTCC) as has been described (24). Endosome-mediated uptake might also play a role, but is poorly understood (25). Iron is then bound to ferritin and transported to lysosomes for degradation and long-term storage in the cardiac myocyte (25). Pathologic iron deposition begins initially within the epicardium and extends to the myocardium and then the endocardium, which helps explain the preservation of systolic function until very late in the disease (1). Once the antioxidant capacity of the cell is exceeded, iron is catalyzed by the rapid Fenton reaction producing hydroxyl ions, which is an extremely reactive free radical species that causes lipid peroxidation producing membrane permeability alterations. These modifications create a leak of hydrolytic enzymes that initiate cell damage and subsequent cardiac myocyte death. In cases with concomitant myocardial ischemia, iron overload can accelerate ischemia-induced reperfusion injury, and may lead to an autocatalytic process that results in a cardiomyopathic process (1,26). Initial evidence suggests that deposition of iron in the sarcoplasm of

epicardial myocytes in this disease is a problem of storage and is not an infiltrative process. Thus, there is the potential for the iron to be removed and for the process to be reversed, which has been the subject of much investigation and has influenced the direction therapeutic interventions have followed (27).

Clinical Presentation

Because of the wide spectrum of etiologies for IOC, symptoms may be quite varied. Early in the disease process, patients may be totally asymptomatic, whereas severely overloaded patients can have terminal irreversible heart failure symptoms. Thus, early identification of the disease becomes a very important consideration. Multiple physiologic, biomolecular, and structural factors such as tachycardia, volume overload, eccentric left ventricular (LV) hypertrophy, endocrinopathies, genetic predisposition, neurohormonal activation, and proinflammatory cytokines can play a role in affecting cardiac function (4,28,29). Patients' initial presentation is often exertional shortness of breath as a result of LV diastolic dysfunction secondary to a restrictive pathophysiology. This condition may later progress to a dilated cardiomyopathy with LV systolic dysfunction (26,30,31). Iron accumulation occurs in the ventricular myocardium before the atrial myocardium (25). Deposition in the conduction system has also been noted (32) and can lead to nodal disease causing bradyarrhythmias and necessitating pacemaker placement. First-degree AV blocks and supraventricular arrhythmias correlate with the extent of iron deposition in the atrial myocardium (33). Iron probably is proarrhythmic by itself (34), and this fact along with the varied deposition of iron in the tissue, leading to nonhomogeneity in conduction velocity or repolarization, may explain the increased incidence of atrial and ventricular tachyarrhythmias that have been noted in subjects with iron overload (35). Paroxysmal atrial fibrillation is the most common form of arrhythmia seen in IOC and is invariably associated with myocardial damage (4). LV dilation with systolic dysfunction predisposes to more frequent ventricular arrhythmias. Moderate to severe LV dysfunction usually occurs with heavy iron deposition. Right heart failure can also be present early in the course of disease and be independent of, or evolve and progress along with, left heart failure. With severe cardiac impairment, average survival is usually <1 year (26,33,36). Iron deposition can also occur in the pericardium and, if extensive enough, result in clinical signs and symptoms.

Diagnosis

A high degree of clinical suspicion is necessary to identify and categorize primary hemochromatosis and secondary iron overload. Diagnosis can be very challenging in the early stages of disease; an accurate assessment of organ-specific iron overload is also helpful in planning treatment.

Biochemical markers. To identify patients with iron overload, plasma transferrin saturation of >55% and serum

Table 1 Etiology of Iron Overload Disorders

Disease	Mechanism	Molecular Correlate	Iron Deposition
Primary			
Hereditary hemochromatosis Type 1 (<i>HFE</i> related) (AR)	Increased GI absorption with normal diet	Missense mutation <ul style="list-style-type: none"> • C282Y homozygosity • H63D homozygosity • C282Y/H63D heterozygosity • Other mutations of <i>HFE</i> 	Liver, heart, endocrine glands
Type 2 (juvenile hemochromatosis) (AR)	Increased GI absorption with normal diet	Mutation on <i>HJV</i> gene, which encodes for hemojuvelin Rare form where hepcidin is inactivated	Liver, heart, endocrine glands
Type 3 (AR)	Increased GI absorption with normal diet	Mutation of transferrin receptor-2	Liver, heart, endocrine glands
Type 4 (AD)	Increased GI absorption with normal diet	Mutation of <i>SLC40A1</i> , which encodes for ferroportin	Macrophages, liver, heart, endocrine glands
Secondary			
a. Iron-loading anemias (transfusion-related)	Transfusion-related	Mutation causing defect in synthesis of α - and β -globin chains of hemoglobin	Heart, pancreas, pituitary, liver
Thalassemia	In severe thalassemia, can have increased GI absorption		
Sickle cell anemia	Transfusion-related	Substitution of a valine for glutamic acid as the 6th amino acid on the beta globin chain (HbS)	Liver, heart
Sideroblastic anemia	Transfusion-related Increased GI absorption with normal diet	Hereditary or acquired Ineffective erythropoiesis	Neurons, heart, mitochondria
Diamond-Blackfan anemia	Transfusion-related	Congenital hypoplastic anemia with decreased erythroid precursors	Heart, liver
Congenital dyserythropoiesis anemia	Transfusion-related	Ineffective erythropoiesis	Liver, heart, endocrine
Post-stem cell transplant patients	Transfusion-related		Liver, heart
Chronic kidney disease/end-stage renal failure/dialysis	Oral and IV iron supplementation Transfusion-related	Decreased erythropoietin	Heart, liver
b. Dietary overload	Increased dietary intake	Increased diet with predisposing genetic factors (proposed mechanism)	Heart, liver, endocrine
African iron overload			
c. Miscellaneous			
Aceruloplasminemia (AR)	Inhibition of iron oxidation	Mutations of ceruloplasmin gene	Liver, brain, pancreas
Congenital atransferrinemia (AR)	Inhibition of iron transportation	Mutations of transferrin gene	Liver, heart, pancreas
Chronic liver diseases			
Hepatitis C and B	In part increased GI absorption	Not applicable	Liver
Alcohol-induced liver disease	In part increased GI absorption	Not applicable	Liver
Porphyria cutanea tarda	In part increased GI absorption	Not established, some are part AD	Liver
Fatty liver disease	In part increased GI absorption	Not applicable	Liver

AD = autosomal dominant; AR = autosomal recessive; GI = gastrointestinal; IV = intravenous.

ferritin of >200 ng/ml or 300 ng/ml (for women and men, respectively) have been proposed as per the 2005 American College of Physicians guidelines (37,38). However, transferrin saturation can miss a substantial population of patients who are homozygous for *HFE* mutations (39). It can also be elevated along with ferritin levels in Asian and Pacific Islanders without the *HFE* mutations, and thus has uncertain significance in these populations (40). Ferritin, being an acute-phase reactant (41), can be elevated in active inflammatory conditions and also in certain liver diseases (42,43). Serum iron studies are a useful tool in screening patients for total-body iron overload, but they are unsatisfactory as a diagnostic tool to detect specific-organ overload such as cardiac iron. The level of serum ferritin at which iron deposition is detected in the heart has not been defined. There are reports of heavy cardiac iron deposition despite the presence of low serum ferritin levels (44,45). Serum iron studies give little information on deposition of iron and less on actual tissue location. In addition, serum ferritin levels in particular have a wide variability when measured serially,

thus making it difficult to use as a marker to determine response to therapeutic interventions.

Tissue biopsy. Tissue biopsy is the traditional gold standard for making the diagnosis of liver iron overload (46), but iron deposition in the heart tends to be patchy (33). Biopsies may thus miss the areas of deposition and provide a false negative result. In myocardial biopsy specimens, the degree and cellular distribution of iron stores known as hemosiderin is best assessed using a Perls Prussian stain, and a semiquantitative assessment of iron stores is derived based on the number of myocytes containing stainable iron (27,47). In normal hearts, no stainable iron should be seen, and as iron overload progresses, the deposition of iron appears to occur in the sarcoplasm starting in the perinuclear areas and disseminating to the entire sarcoplasm (27,33,36,48). The iron concentration can be measured with atomic absorption spectrometry, and Olson et al. (48) have reported the average elemental iron in biopsy specimens are 399 $\mu\text{g/g}$ dry weight in normal subjects and 1,701 $\mu\text{g/g}$ dry weight in idiopathic hemochromatosis, with significant

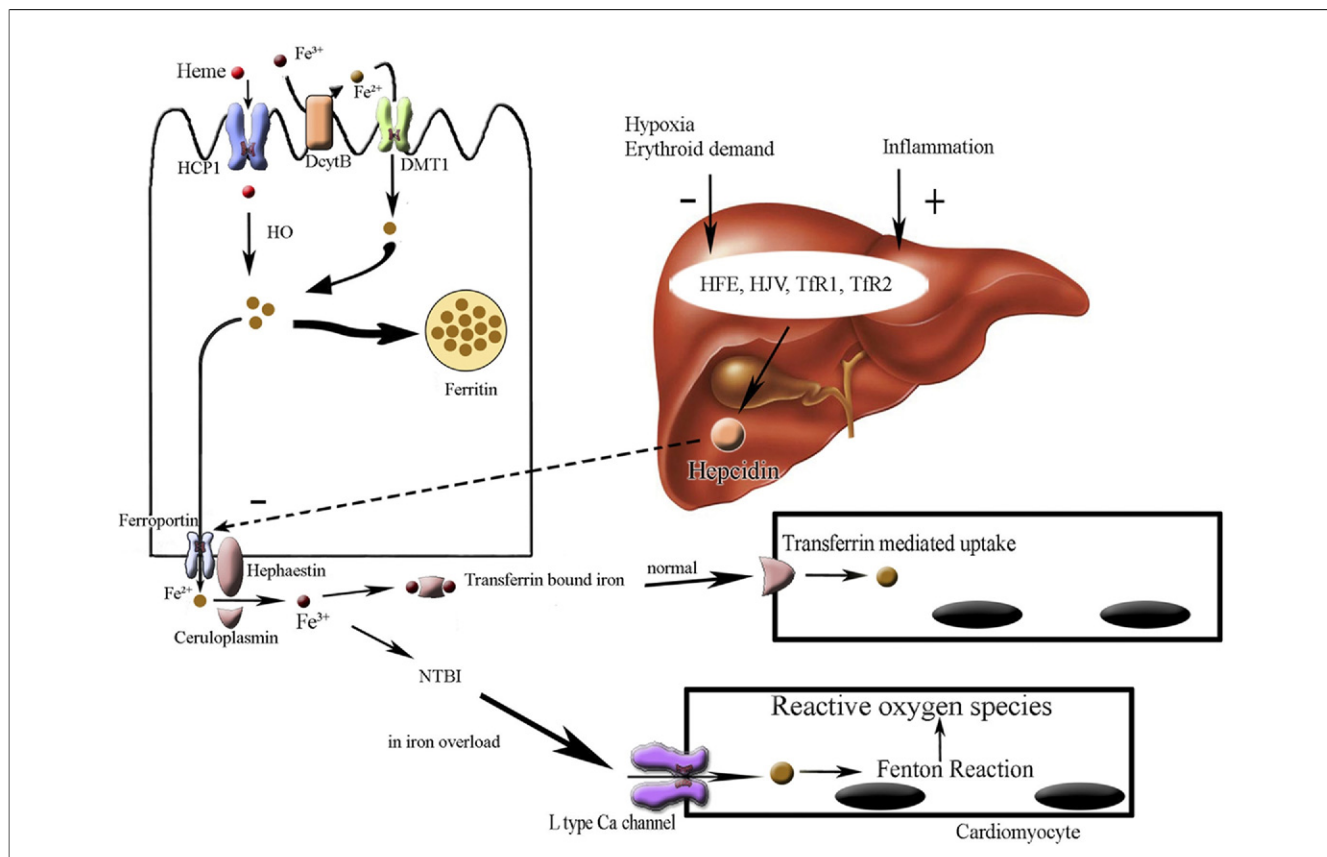


Figure 1 Iron Kinetics

Heme is absorbed by Heme carrier protein (HCP)-1 and released from iron by hemoxygenase (HO)-1, but heme uptake overall still remains controversial. Non-heme iron is reduced by duodenal cytochrome b at the apical membrane of intestinal enterocytes (21), which is taken up by intestinal epithelium by the divalent metal transporter (DMT)-1 (22,23). Ferrous iron is then transported to the basolateral portion of the cell by iron carriers and later transported into the circulation by the duodenal iron exporter Ferroportin (regulated by hepcidin) when there is a need for iron. Ferrous iron is oxidized by ceruloplasmin in non-intestinal cells and also by a homolog of ceruloplasmin, Hephaestin, in intestinal cells to ferric iron and loaded on to transferrin. With the increase in intracellular concentrations of iron, ferritin synthesis also increases. Once the storage capacity is exceeded, metabolically active iron is released intracellularly in the form of hemosiderin and toxic nontransferrin-bound forms of iron (NTBI).

overlap between these 2 groups. A positive result indicates that iron overload is present, but not how extensive the process may be (27,36). Also, biopsy is an invasive procedure and, as a result, is not an ideal tool to screen asymptomatic patients.

Echocardiography. As iron overload proceeds, echocardiography may reveal biventricular dilation and progressive evidence of a restrictive cardiomyopathy from myocardial damage (49). Echocardiographic evidence of ventricular diastolic dysfunction can be detected early before systolic dysfunction occurs, specifically using tissue Doppler signals (50,51). Lambardo et al. (52) failed to identify diastolic dysfunction using conventional Doppler echocardiographic parameters such as mitral inflow E/A ratio and deceleration time to predict the severity of myocardial iron overload verified by myocardial biopsy in thalassemia patients with preserved LV systolic function. Later, however, Vogel et al. (53) reported that a decrease in peak systolic and peak diastolic early-filling tissue Doppler wave is frequently seen in the patients with β -thalassemia and cardiac magnetic

resonance imaging (MRI)-proven myocardial iron overload, and that these declines are more prominent in the LV septum than lateral free wall. Tissue Doppler-derived peak systolic strain has similarly shown to decrease in that population (54). Palka et al. (50) has reported a decrease in peak systolic and diastolic early filling mitral annular tissue velocity as well as prolongation of the duration of atrial reversal wave of pulmonary vein Doppler in HH patients with predominantly normal LV systolic function. In our previous investigation in asymptomatic HH subjects, echocardiography has detected enhanced left atrial active contraction even before overt LV diastolic dysfunction appeared, and this may be the earliest detectable echocardiographic finding of cardiac iron overload in this population (55). Interestingly, diastolic strain rates, measured with color-coded tissue Doppler in subjects with iron overload, appears to be related to the level of oxidative stress (56), indicating that these echocardiographic parameters may be a surrogate for iron overload-induced oxidative stress (57).

It could be hypothesized that cardiac contractile reserve is impaired in IOC before detectable LV systolic dysfunction occurs at rest, and this abnormality might be detected by stress echocardiography. We have tested this hypothesis in asymptomatic HH subjects, and found that contractile reserve is not decreased in this population as compared with age- and sex-matched normal volunteers who lacked HH mutations (58). However, unexpectedly, a higher incidence of ischemic stress electrocardiographic responses in HH subjects (33%) compared with normal subjects (10%) was observed. The significance of this finding is unclear, but highlights the necessity of stress echocardiography or other stress imaging when evaluating coronary artery disease in this population (58).

As a result of these considerations, echocardiography has the potential to identify early pathophysiology due to iron overload, although it is not sensitive enough to reveal actual iron deposition in tissues. In addition, echocardiography has been successfully employed to evaluate iron-depleting therapy in idiopathic hemochromatosis as it demonstrated a decrease in the LV mass and wall thickness, and these findings correlated with the reversal of myocardial iron infiltration (59).

Computed tomography (CT). CT scanning can identify high electron density iron in the organs (60,61), but its sensitivity and specificity are poor with high false positive rates associated with fibrosis (62), and it has a low sensitivity for detecting the early stages of iron overload in tissues (63). The clinical usefulness of this diagnostic method for IOC has not been tested.

MRI. MRI is the only presently available noninvasive method with the potential to assess quantitatively myocardial iron load. MRI constructs images from transmitted microwave signals induced by exciting protons in the body in a high magnetic field. In noniron-overloaded hearts, these signals are homogenous, and relaxation time (time to fade excited signals) lasts for a longer duration (brighter over time). In iron-overloaded hearts, however, the iron paramagnetic effect produces changes in MR signal intensity and susceptibility, and shortens the relaxation time and darkens the image more quickly (64). MRI scanning can refocus the signals returning from the tissues, using a special radiofrequency pulse (spin echo [SE]) or by using special small magnetic fields called gradients (gradient echo [GE]) at specific time intervals (echo time [TE]). The time constant of decay for SE-induced relaxation time is known as T2 and for GE is T2*, and the units are in milliseconds (ms). Iron in the tissue shortens the relaxation time (signals fade faster with more iron content), thus, the more the iron content, the shorter are the T2 and T2*. Some investigators report rates of signal decay ($R2 = 1,000/T2$ and $R2^* = 1,000/T2^*$), which are reciprocals of T2 and T2*, respectively, and are measured in Hertz or s^{-1} . Earlier studies for quantitative evaluation of the iron content were performed using the SE measurement, and it was noted to have an inverse relation with liver iron concentration (65–67). SE

has a poor signal-to-noise ratio at longer echo times, and, with its limited sensitivity, is unsatisfactory to make the accurate quantification of myocardial iron (65,66,68,69). On the other hand, GE techniques, which do not have these problems, seem to be more suitable for assessing myocardial iron content. Anderson et al. (70) were the first to use the T2* technique for myocardial iron assessment in subjects with thalassemia major. In that study, a single short-axis midventricular slice was acquired at 9 separate TEs, and each slice was acquired during 1 breath hold of approximately 20 s (Fig. 2). It was observed that there was a progressive decline in ejection fraction as the myocardial iron deposition increased, and all patients with ventricular dysfunction had a myocardial T2* of <20 ms (71). The coefficient of variation for interstudy reproducibility of cardiac T2* was 5%. The scanning time of T2* was recently shortened by the use of a multi-GE technique that has the advantage that all slices are acquired in just 1 breath hold (72). Pepe et al. (73) used a multislice multi-GE T2* technique to achieve segmental analysis of LV myocardial iron content and observed a good correlation between the global T2* (12 segments) and T2* value in the midventricular septum. They concluded that the midventricular T2* value was a good marker of the entire myocardial iron content. However, they were concerned that midventricular T2* would not be sensitive enough to reflect the heterogeneity of composition of myocardial iron overload (cytosolic iron, hemosiderin deposits, and so on) (69,73–75). In contrast, the T1-/T2-weighted SE method has been proposed as being more sensitive in differentiating cytosolic iron and ferritin (76). Recent optimized breath-hold T2 imaging has shown improved local interstudy reproducibility and intersite reproducibility, with coefficients of variance of 4.4% and 5.2%, respectively, as compared with the traditional T2* imaging (77). One potential advantage of newer T2 imaging will be to perform a multisegment analysis to explore regional distribution of myocardial iron. The accuracy of T2* imaging is currently limited to the septum due to susceptibility effect artifacts from anterior and posterior cardiac veins and lungs that contaminate images of the other LV regional walls. In addition, measuring both T2 and T2* might be beneficial, if different forms of tissue iron might be respectively defined by T2 and T2* measurements (77).

Furthermore, cardiac MRI can provide accurate reproducible measures of LV systolic ejection fraction, volumes, and mass that can be followed over the course of therapy (78). A correlation between the decline in LV ejection fraction and higher myocardial iron content measured with T2* has been noted (79–81). Attempts to assess LV diastolic function in IOC with cardiac MRI using tagging (82) or displacement encoding with stimulated echoes (DENSE) sequence (83) is currently under investigation.

In summary, GE T2* technique is still widely used for clinical assessment of entire iron content in IOC; however, the new technical development of cardiac MRI will likely

provide methods for more detailed quantification and characterization of deposited iron species in IOC.

Proposed Clinical Pathway to Evaluate for IOC

As a result of our experience with patients with cardiomyopathy, we currently propose the following clinical pathway to evaluate for IOC. This pathway is currently being used by the National Institutes of Health Clinical Center Cardiology Consult Service (Fig. 3).

If the patient is known to be at risk for iron overload due to a previous genetic diagnosis of HH or multiple RBC transfusions, transthoracic echocardiography with complete LV diastolic function assessment including tissue velocity measurements of the mitral annulus should be conducted every 1 to 2 years. This evaluation should occur regardless of cardiac symptoms or biochemical evidence of iron overload. If either abnormal LV diastolic function and/or decreased peak systolic tissue velocity of mitral annulus are noted, cardiac MRI with T2* assessment following the grading system based on the T2* measurements listed in the following text should be performed. In cases where idiopathic cardiomyopathy is the primary diagnosis, regardless of iron study results, we recommend cardiac MRI with T2* measurements to rule out IOC since it has been reported to occur with normal iron levels (44,45) and is a treatable condition. Once cardiac T2* is confirmed to be normal (>20 ms), it is unlikely that IOC will become a cause of idiopathic cardiomyopathy unless the patient is at risk for IOC and develops it in the future.

Conventional Therapy

Iron overload is a slow, cumulative process; early diagnosis and treatment should be the main goal of therapy to prevent multiorgan failure. Standard treatment currently includes dietary management, phlebotomy, and chelating agents. At present, research using calcium channel blockers (CCBs) in IOC, gene therapy to target the genetic mutations in thalassemia and sickle cell disease, and heart transplantation in refractory heart failure are under intense scrutiny.

In order to assist with clinically grading the severity of IOC at this time, people at risk for IOC may be divided into 3 categories based on cardiac T2* values (64):

- 1. Those with T2* >20 ms (green zone) are at low risk for the imminent development of congestive heart failure.
- 2. Those with T2* between 10 and 20 ms (yellow zone) in whom cardiac deposition has probably occurred are at intermediate risk of cardiac decompensation.
- 3. Those with T2* <10 ms (red zone) are in the high-risk category of cardiac decompensation and need immediate review and intensification of chelation therapy.

Although the diagnostic use of cardiac MRI for IOC has been established, the validity of T2* obtained from cardiac MRI as a therapeutic marker is still under investigation. Thus, proper guidelines to follow for evaluating the therapeutic effects of IOC treatment with cardiac MRI measurements still need to be developed.

There is some evidence that with the use of effective chelation therapy, the development of clinically significant cardiac iron overload in patients in the green and yellow zones may be delayed (59,84,85). It is apparent that patients

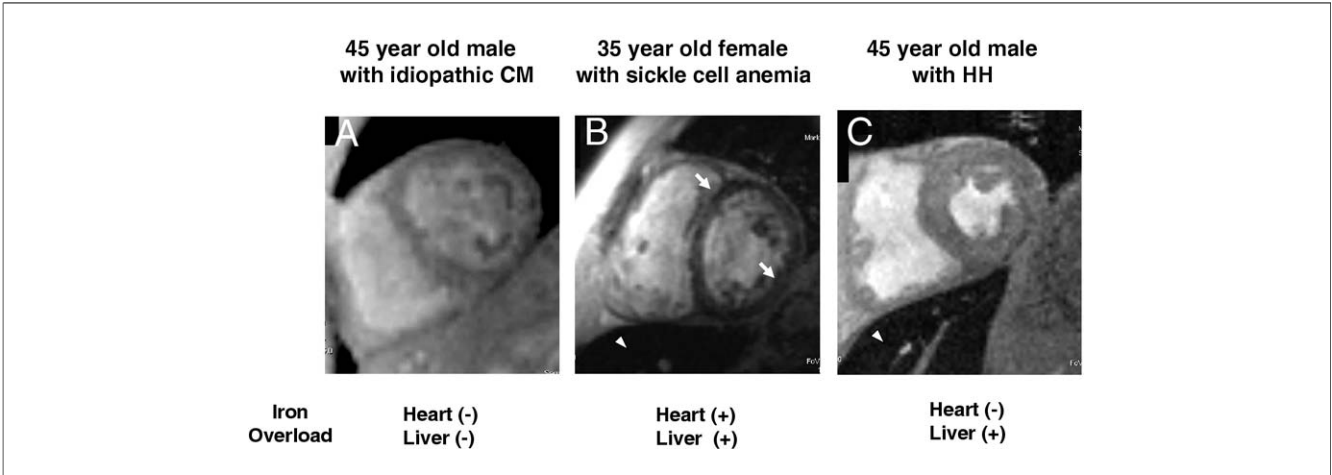


Figure 2 Typical Examples of T2* Cardiac MRI Imaging to Assess Both Myocardial and Liver Iron Overload

T2* images were obtained by using the gradient echo sequence of cardiac magnetic resonance imaging (MRI) employing a 1.5-T scanner as reported by Anderson et al. (70). The images captured at TE time of 5 ms are shown. T2* image of a 45-year-old with idiopathic cardiomyopathy (CM) shows no evidence of iron overload in the liver and heart (A; heart T2* = 39 ms; liver T2* = 27 ms). T2* image of a 35-year-old female with sickle cell anemia and a history of multiple transfusions shows iron overload in both the liver (arrowhead) and heart (arrows) (B; heart T2* = 12 ms; liver T2* < 2 ms). T2* image of a 45-year-old male with hereditary hemochromatosis (HH) shows iron overload seen in the liver (arrowhead), but not heart (C; heart T2* = 30 ms; liver T2* = 2 ms). Please note that iron-overloaded tissues appear darker in the images. (The images in this figure were provided by Andrew Arai, MD, Branch of Cardiac Energetics, National Heart, Lung, and Blood Institute of the National Institutes of Health, Bethesda, Maryland.)

in the red zone with heart failure symptoms need to be treated with aggressive chelation therapy in conjunction with standard heart failure medications including angiotensin-converting enzyme inhibitors, diuretics, and beta-blockers. It remains to be seen whether the addition of chelation therapy will either stop the progression of or improve LV dysfunction beyond what might be accomplished by aggressive standard heart failure treatment.

Dietary management. Dietary interventions to minimize or eliminate iron ingestion are not feasible and are usually unnecessary as only 0.5 to 1.0 mg of iron is absorbed daily in excess of normal absorption in most persons with hemochromatosis, and the total daily absorption is small in comparison with the 200 to 250 mg of iron per unit of blood removed weekly by therapeutic phlebotomy. Diets do not enhance iron excretion, and patients must understand that there is no substitute for iron depletion therapy (86). Patients can eliminate the consumption of iron-rich foods such as red meat and still have little effect on total body iron content. Alcohol increases iron absorption and should be minimized (87). Multivitamin tablets containing iron and vitamin C should be avoided (88). Tannates, phytates, oxalates, calcium, and phosphates present in food can bind iron and inhibit its absorption, which provides little benefit (89).

Phlebotomy. Phlebotomy, the gold standard for treating HH, causes iatrogenic anemia by removing 400 to 500 ml of blood (200 to 250 mg of iron) at each session, thus

mobilizing iron from the organs where it is stored for the production of hemoglobin. Early in the disease, this procedure may be done up to 1 or 2 times a week to obtain a target ferritin below 20 ng/ml (90,91). Once the therapeutic ferritin level is achieved, the frequency of maintenance phlebotomy is determined with periodic follow-up of serum iron and ferritin levels with gradual decreasing phlebotomy interval. Generally, maintenance phlebotomy requires phlebotomy 3 to 4 times a year for men and 1 to 2 times for women (92). Routine monitoring of hemoglobin, ferritin, and hematocrit is essential during maintenance phlebotomy (93). Improvements in cardiac function in HH patients with cardiomyopathy and refractory arrhythmias have been noted with aggressive iron removal with phlebotomy, especially when started early in the disease process (94–96).

Chelating agents. Phlebotomy is not feasible in patients who have significant anemia or malignancy, and in some with hemodynamic instability. In such cases, chelation therapy has been effectively used as an alternative. The goal of chelation therapy is to detoxify those organs containing excess iron by binding the iron, removing it, and then excreting the compound in urine and bile. Presently available chelators include deferoxamine, deferasirox, and deferiprone.

Deferoxamine is a clinically approved, highly specific hexadentate iron-chelating molecule that binds to iron released from the reticuloendothelial system, which has scavenged iron after the catabolism of senescent RBC, and

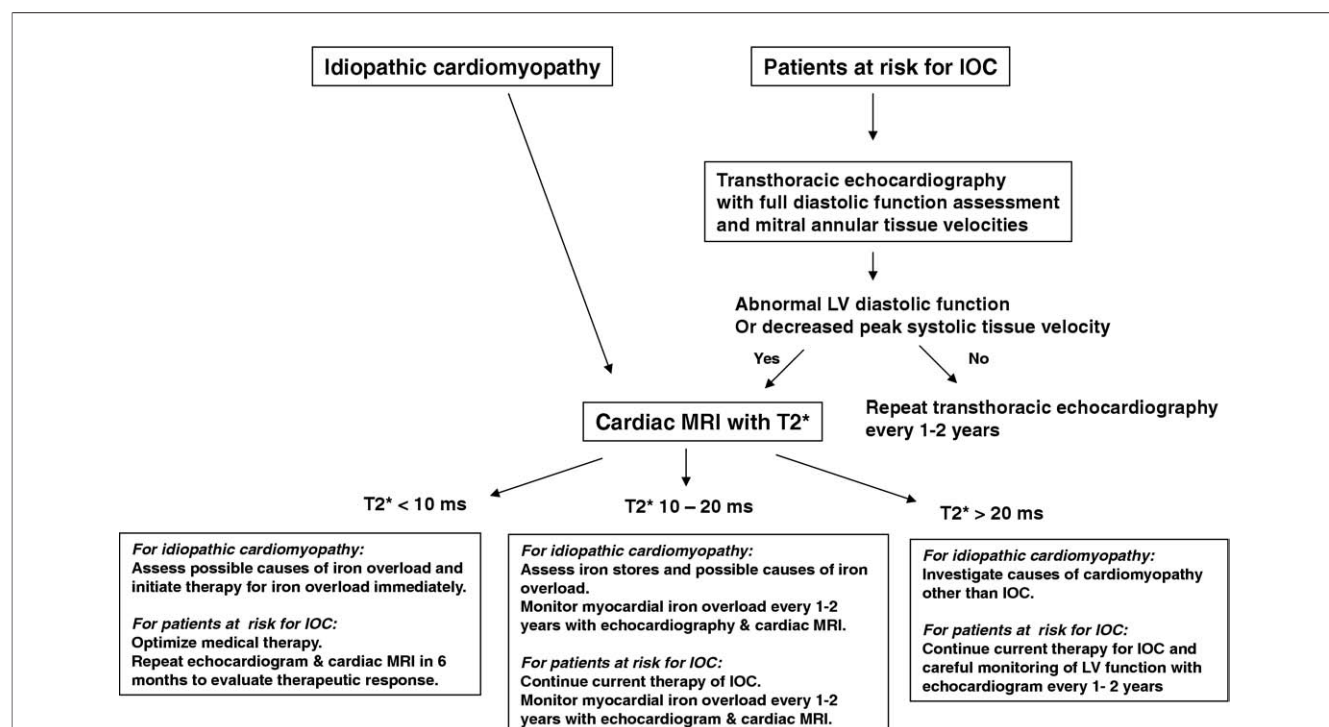


Figure 3 Our Proposed Clinical Pathway to Evaluate Patients With Idiopathic Cardiomyopathy or Those at Risk for Iron Overload

IOC = iron overload cardiomyopathy; LV = left ventricle; MRI = magnetic resonance imaging.

excretes it in the urine. It also has a very high affinity to bind with the trivalent ferric ion and is thought to remove cardiac iron by direct interaction with this ion. The benefits of long-term subcutaneous deferoxamine therapy of increasing survival and decreasing cardiac complications in transfusion-dependent, iron-overloaded thalassemia patients is well documented in the medical literature (2,83,97,98). High intravenous doses, instead of traditional subcutaneous infusion, are also used for the rapid removal of cardiac iron from heavily iron-loaded patients with cardiac failure (84). Prospective studies confirming the beneficial effect of intravenous deferoxamine in the reduction of myocardial iron content in IOC were reported in patients treated with intravenous deferoxamine for 12 months with MRI-derived T2* (99). Reduction in iron levels was associated with an increase in T2* MRI values (5.1 ± 1.9 ms to 8.1 ± 2.8 ms, placebo vs. deferoxamine, $p = 0.003$), significant improvements in LV ejection fraction ($52 \pm 7.1\%$ to $63 \pm 6.3\%$, $p = 0.03$), and reductions in LV volume and LV mass index. Unfortunately, deferoxamine has a high maintenance cost, poor oral bioavailability, and the need for frequent administration. These considerations often contribute to poor compliance in patients (100).

Deferiprone is a bidentate chelating agent with good oral bioavailability and rapid absorption from the stomach, which reaches peak levels in 2 h after administration after being metabolized in the liver. It is being tested on β -thalassemia and sickle cell patients with transfusion iron overload, and its long-term efficacy and safety have not been fully established (93). In the U.S., it is available only through the Food and Drug Administration treatment use program. Clinical efficacy of deferiprone is less consistent than deferoxamine (101,102). In a randomized, double-blind, placebo-controlled trial in 65 patients over 12 months, subcutaneous deferoxamine combined with oral deferiprone therapy reduced myocardial iron and improved the ejection fraction and endothelial function in thalassemia major patients with mild to moderate cardiac iron load when compared with deferoxamine therapy alone (103).

Deferasirox is a tridentate lipophilic oral chelating agent that selectively binds to iron in the ratio of 2:1 and mobilizes iron from stores. The early benefit of using deferasirox has been demonstrated in thalassemia, sickle cell disease, myeloproliferative disorders, and Diamond-Blackfan anemia. Results from small-scale, randomized phase III trials evaluating the effect on iron overload have been encouraging (104,105). Despite these hopeful results, long-term safety and efficacy beyond 1 year is lacking at this time. Thus, there are insufficient data at present to support the use of deferasirox to treat IOC.

Newer chelating drugs. Deferitritin, desferriethiocin, hydroxybenzylethylenediamine-diacetic acid, pyridoxal isonicotinoyl hydrazone, 2-pyridylcarboxaldehyde 2-thiophenecarboxyl hydrazone, and L1NA-II (a deferiprone derivative) are among the newer chelating agents that are under active investigation. A drug with satisfactory oral bioavailability and good long-

term efficacy and safety would be extremely useful, and a quest for such an agent is ongoing.

Erythrocytapheresis. Erythrocytapheresis involves an automated exchange of RBCs of patients with hemochromatosis with those of subjects without and thus helps in decreasing the iron overload mainly in the form of hemoglobin (106,107). This procedure is mainly used in treatment and prophylaxis of sickle cell patients by removing the sickle cells and also old RBCs (107). This is a complex and costly procedure with a high risk of infection, and further research is needed to prove its efficacy for IOC (108).

Heart transplant. If a patient has reached stage IV New York Heart Association functional class heart failure symptoms without any improvement in heart failure despite aggressive medical therapy including cardiac resynchronization therapy, heart transplantation may be a reasonable option to extend survival and improve quality of life. If heart transplantation becomes a serious consideration, it must be performed in combination with the aggressive application of therapy to reduce iron overload. Recently, Caines et al. (109) published a review of 16 IOC end-stage heart failure patients who received heart transplantation from 1967 to 2003, with a mean age of 31 years (age range 14 to 63 years). They had a actuarial 10-year survival rate of 41% with Kaplan-Meier analysis, with 1-, 3-, and 5-year survival rates of 81% for all 3 time intervals (109). Three patients died within 1 year secondary to infectious complications. Thirty-day mortality was 12% (109). When severe IOC and hepatic iron overload coexist, combined heart-liver transplantation may be considered because transplantation of only a single organ might not improve the outcome (109). There are a limited number of cases available in the literature, and thus more data are needed to validate whether heart transplantation actually improves the clinical outcome of patients short and long term.

Newer Mechanistic Directed Therapeutic Options

Role of CCBs. The mechanisms of iron transport into excitable tissues such as cardiac myocytes are under active investigation. Non-transferrin-bound iron enters the heart in the ferrous form, and the rate of transport increases with augmentation of the iron load (110). Recent evidence has suggested that voltage-gated LTCC may be involved with iron transport into cardiomyocytes. LTCC primarily transport Ca^{2+} , but can also transport other divalent ions such as Fe^{2+} and Zn^{2+} (24,111). The association of LTCC with iron uptake is evident in studies that have shown: 1) an increase in iron uptake rates in excitable tissues, i.e., tissues with pacemaker qualities, compared with nonexcitable tissues as they have more LTCC (110,111); 2) an increased activity of LTCC with increased levels of iron (111-114); and 3) LTCC agonist Bay K 8644 produced a 2.3-fold increase in the nifedipine-sensitive Fe^{2+} uptake by the heart by enhancing LTCC activity (24). More definitive evidence of the role of LTCC in iron overload was found when Oudit

et al. (114) used therapeutic levels of the LTCC blockers verapamil and amlodipine to treat IOC in mice, and demonstrated that treatment with CCBs inhibited the LTCC current in cardiac myocytes, thereby attenuating myocardial iron accumulation and oxidative stress, improved survival, prevented hypotension, and preserved heart structure and function. It was also noted that iron-overloaded transgenic mice with cardiac-specific overexpression of the LTCC $\alpha 1$ -subunit had 2-fold higher myocardial iron and oxidative stress levels, as well as greater impairment in cardiac function. LTCC blockade in these mice protected them from iron overload. The above findings indicate the possible preventive and therapeutic roles of CCBs in IOC (114). If effective, they may be used in the early stages of IOC, and may also enhance the therapeutic effects of standard chelation therapy. The role of verapamil, but perhaps not the dihydropyridine CCBs, may be limited in the advanced stage of IOC, which may be associated with conduction system defects and LV systolic dysfunction, both of which may be exacerbated by verapamil administration. Presently, a nonrandomized, open-label trial sponsored by the National Institute of Diabetes and Kidney Disease is underway to assess the role of nifedipine in iron overload patients.

Hepcidin. The human hepcidin gene *HAMP* located on chromosome 19 encodes for a precursor protein, 84-amino acid preprohepcidin, which is primarily produced in the liver. It undergoes subsequent post-translational processing that results in a mature 25-amino acid form, hepcidin, which plays a major role in regulating iron homeostasis in the body. The evidence for this conclusion was observed in hepcidin knockout mice that developed massive iron overload (115) as well as in mice engineered to overproduce hepcidin who developed severe anemia (116). Hepcidin binds to ferroportin, resulting in internalization and degradation of ferroportin, thereby blocking cellular iron export (117,118). This obstruction results in a decrease in serum iron levels by blocking iron absorption from the intestine, iron recycling from macrophages, and mobilization of stored iron from liver hepatocytes. Hepcidin is thought to be regulated by hemojuvelin, transferrin receptor-2, transferrin, the *HFE* gene, hypoxia, inflammation, and erythroid factors (119). Besides production by the liver, hepcidin is also believed to be produced by macrophages (120), fat cells (121), and the heart (122). Lower levels of hepcidin were observed in studies on HH (123,124) and nonhemochromatosis iron overload diseases (125–127), so hepcidin analysis might provide a role in screening, monitoring, prognosis, and therapy of HH. Techniques using mass spectrometry can identify various isoforms of hepcidin in urine and serum (128,129). Augmentation of hepcidin levels by iron reduction, hepcidin inducers, hepcidin supplements, and antioxidants may play a role in the future treatment of iron overload conditions. There is still a lot to understand about the full potential of this key regulator of iron homeostasis, and additional studies are

underway and are needed to determine its role in iron regulation.

Role of gene therapy. Curing primary genetic diseases such as β -thalassemia and sickle cell disease before or after tissues develop iron overload could be an option to prevent IOC. Gene therapy involves correction of the underlying defect by genetically modulating autologous stem cells, which are then implanted by a vector into the target cell, thereby facilitating the expression of the desired functional product by the target cells. Lentiviral vectors proved capable of efficiently transmitting complex globin expression cassettes containing transcriptional regulatory sequences from the β -globin locus control region, which are required for high-level expression, to treat β -thalassemia (130). Correction of anemia and organ damage in β -thalassemic mouse models has been achieved using both β -globin (131,132) and γ -globin vectors (133,134). Recently, Pestina et al. (130) reported the use of a γ -globin lentiviral vector for hematopoietic stem cell transduction in severe sickle cell disease. Similar gene therapy approaches designed to target overexpression of hepcidin and inhibition of DMT-1 expression, ferroportin expression, and expression of the wild-type *HFE* gene using duodenal stem cells have been postulated to greatly reduce the iron accumulation in HH and are yet to be evaluated in mouse models of HH (135). Although the approach of gene therapy is promising, these techniques have relatively high morbidity and mortality rates, and extensive biosafety research is needed to demonstrate that the benefit-to-safety ratio is acceptable before it can be accepted as a mainstream medical treatment of IOC. These studies are presently being pursued.

Role of stem cell transplantation. It is also hoped that introduction of healthy hematopoietic stem cells in severe congenital anemia lacking appropriate β -hemoglobin production, such as sickle cell disease or β -thalassemia, may reverse the primary pathophysiology in the disease and reduce the need for transfusions (136). This approach, however, presently is not ready for widespread application because stem cell transplantation requires aggressive chemotherapy and radiation unless perfectly matched donor cells are available. Currently, clinical trials are underway to test low-intensity radiation along with immunosuppressant drugs without chemotherapy to accomplish successful stem cell transplantation with a half-matched donor in order to broaden its use.

Conclusions

IOC is a potentially lethal, but treatable disease when diagnosed and treated early in its course. Newer insights into iron homeostasis and the complicated mechanism of iron entry into the heart are now emerging. Improved cardiac imaging techniques are being developed and perfected for the early identification of iron overload and its treatment. New therapeutic options with better chelating agents with increased safety, efficacy, and absorption, with

therefore better compliance, are being evaluated. The role of CCBs, hepcidin, and genetic and stem cell therapy are being investigated and may play a role in future disease management. Further studies are needed to define optimal medical care for increasing survival and improving quality of life for these patients. In the interim, it is important to use the techniques presently available for early diagnosis and to utilize the existing therapeutic interventions in a safe manner.

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